



Cost effectiveness of vismodegib (Erivedge®) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma and locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost effectiveness of vismodegib (Erivedge®) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma (mBCC) and locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy. The NCPE does not recommend reimbursement of vismodegib (Erivedge®) at the current price.

The HSE has asked the NCPE to carry out an assessment of the manufacturer's (Roche) economic dossier on the cost- effectiveness of vismodegib (Erivedge®) in the treatment of mBCC and laBCC inappropriate for surgery or radiotherapy. The NCPE uses a decision framework to systematically assess whether a technology is cost effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examine all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

In September 2013, Roche Products (Ireland) Limited submitted an economic dossier on the cost-effectiveness of vismodegib (Erivedge®) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma (mBCC) and locally advanced basal cell carcinoma (laBCC) inappropriate for surgery or radiotherapy. There is a high unmet need for therapies in advanced BCC, particularly in those with metastatic and severely mutilating locally advanced disease. With the exception of vismodegib, there is no other licensed therapy and very little evidence of benefit from unlicensed therapies. Vismodegib is a small molecule inhibitor of the hedgehog signalling pathway and is available as a once daily 150mg capsule for oral administration. Conditional marketing authorisation was granted by the European Commission in July 2013 subject to the submission of additional efficacy data on mBCC and periodic safety updates.

1. The economic evaluation compared vismodegib with current standard of care. In these patients, surgical and active treatment options are limited and standard of care is assumed to comprise of best supportive care (BSC) (i.e. psychological support and wound care). A three-state Markov model, incorporating progression-free survival (PFS), progressive disease and death, was used to perform a cost-utility analysis. The effects of treatment on other potentially important intermediate endpoints such as tumour shrinkage or locoregional control are not represented in the model.
2. The safety and efficacy of vismodegib was evaluated in a pivotal phase II, multicentre, single-arm, non-randomised, open-label, two-cohort trial which included 33 patients with mBCC and 63 patients with laBCC. The primary outcome was objective response rate (ORR) as assessed by independent review. Investigator-assessed ORR was included as a secondary endpoint. PFS and overall survival (OS) were also included as secondary endpoints but considered suboptimal endpoints to measure clinical benefit. The primary analysis (9 months after the last patient enrolled) reported an independently-assessed ORR of 30.3% in mBCC (95% CI 15.6% to 48.2%, all partial response) and 42.9% in laBCC (95% CI 30.5% to 56.0%, 21% complete response, 22% partial response). The median duration of objective response was 7.6 months in both cohorts, and the PFS was 9.5 months. Data on OS were not mature.

3. The primary endpoint, ORR, was not used to inform the company's economic model. PFS and OS data from this study were used to determine transitions between the PFS and progressive disease health states, and death in the model. There is no comparative efficacy data for vismodegib versus supportive care or other active comparators, and no evidence on the natural history of the disease using historical or observational data has been presented. It is not possible to assume that the observed activity in the single-arm study could result in a clinically relevant benefit in terms of PFS or OS. Significant numbers of patients are lost to follow-up for the PFS and OS analysis at later stages of the study.
4. All patients in the pivotal phase II study had at least one adverse event; the majority were of grade 1-2 (57.7%). The most commonly occurring adverse events were muscle spasms (68.3%), alopecia (63.5%), dysgeusia (51.0%), weight loss (46.2%), fatigue (35.6%) and nausea (28.8%). Other common events are diarrhoea and constipation in around 20% of patients. Venous thromboembolic events, second primary malignancies and keratitis are identified as potential risks which will be followed up in an ongoing safety study. 51% of patients who had received the drug had discontinued treatment at the primary analysis cut-off. 72% of patients had discontinued treatment at the 12 months update.
5. The NCPE review group had concerns regarding the progress of patients through the disease model. All patients receiving vismodegib were assumed to start in the PFS health state and were at risk of moving to progressive disease or death in each model cycle, whereas all patients in the BSC arm were assumed to start in the progressive-disease health state and can only progress to the dead state in each model cycle. This structural assumption confers PFS and OS advantages on vismodegib and introduces significant bias in favour of vismodegib treatment.
6. BSC was assumed to comprise of quarterly outpatient visits for patients in the PFS health state, and monthly visits for patients with progressive disease, based on an Irish-physician questionnaire. SF-36 quality of life data was

collected during the pivotal phase II study but not used in the model. Instead, QALYs were valued using utilities measured in a time trade-off (TTO) study conducted by the company. There was no patient involvement in the development of the TTO study vignettes which were not based on trial outcomes and which did not incorporate treatment-related adverse events.

7. The company model estimated the cost-effectiveness of vismodegib over the lifetime of the cohort and reported the incremental cost-effectiveness of vismodegib compared with BSC. Separate scenarios were submitted using independently-assessed (assessed 12 months after the initial analysis) and investigator-assessed (assessed 18 months after the initial analysis) PFS and OS data. The NCPE review group considered the results of the economic model based on the independently-assessed outcomes to be more appropriate than the investigator-assessed outcomes. ICERs based on the independently-assessed outcomes were €556,657 per QALY in laBCC and €240,902 per QALY in mBCC. The assumption of a survival benefit with vismodegib is the main driver of the mBCC model. When the assumption of “no survival benefit” is made, the ICER increases to €942,357 per QALY. The impact of adverse events on patients’ quality of life was not considered in the model and would be expected to further increase the cost per QALY for vismodegib compared with BSC. One-way and probabilistic sensitivity analyses were conducted for both cohorts. Variables adjusted in univariate sensitivity analyses included discount rate, time horizon, health state utilities, BSC costs, and adverse events costs. Of these variables, changes to the health-state utilities had the biggest impact on the results. The probability that vismodegib is cost-effective at a willingness to pay threshold of €45,000 per QALY is 0% for both the laBCC and mBCC cohorts.
8. The place in therapy of vismodegib is uncertain, due to the subjectivity associated with the definition of “advanced BCC...inappropriate for surgery”. Roche estimated that 51-57 patients will be diagnosed with advanced BCC annually, between 2014 and 2018, and estimate a budget impact peak of €3.6 million per annum in 2016 and a cumulative five-year budget impact of €14.7 million. The median treatment duration of vismodegib in the phase II trial was

14.1 months which, at the price currently being sought for vismodegib, would cost approximately €92500 per patient.

9. There were significant limitations associated with the submission, the most critical being the lack of evidence for additional benefits of vismodegib in prolonging PFS and OS compared with supportive care. Based on the results of this economic evaluation, the NCPE does not recommend reimbursement of vismodegib.